

EXHIBIT 1

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Shacknai, et al

Serial No. 10/829,426

Attorney Docket No.: 00-40175-US-P2DC

Filing Date: April 21, 2004

COMPOSITIONS AND METHODS
FOR HIGH SORPTION OF SKIN
MATERIALS AND DELIVERY OF
SULFUR

DECLARATION OF HOWARD MAIBACH, Ph. D.

I, Howard Maibach, Ph.D., do hereby declare that:

1. I am aware that the U.S. Patent and Trademark Office Examiner has rejected the above-identified patent application because the Examiner believes that sulfur may be toxic above a concentration of 6%.
2. The Examiner cited my July 1990, letter to the editor in the Journal of the American Academy of Dermatology, pgs 155-57, as evidence supporting this.
3. I respectfully must advise you that it was not my intent in this article to indicate that sulfur is toxic when applied topically at a concentration above 6%.
4. I was discussing an earlier report that topical sulfur had been "toxic" when applied at 6%, probably under occlusion, to an infant. This reported "toxicity" in this case may have been due to other causes or due to the exceptional, higher permeability to absorption of infant skin compared to that of young children and adults.
5. It was my intent then, and my opinion now, that sulfur has been safely applied topically, literally for centuries, at many concentrations, including those over 6%.

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8. Sulphur is a "traditional" component of topical medications and has been used over many years for disorders such as acne, seborrheic dermatitis, rosacea, scabies, pediculosis and ringworm.
9. Although new drugs have superseded the use of sulphur in many instances, sulphur is still the preferred choice of some clinicians in some patients, particularly those with stubborn and recalcitrant disorders.
10. I have prescribed sulphur containing medications in recent months for patients with persistent seborrheic dermatitis of the scalp and recalcitrant comedonal acne.
11. I am presently aware of the published letter entitled "Sulphur Revisited" by Maibach, Surber and Orkin (J. Am. Acad. Derm. 1990 23:154-5) which refers to the early work of Basch (Arch Exp. Pathol. Pharmacol. 111:126-132) and Rasmussen (Year Book of Dermatology, Chicago 15-38) whose work suggested that fatal toxicity in children was purported to have occurred after use of sulphur containing topical preparations in the treatment of scabies. Maibach et al., however, state "[w]e and others have used precipitated sulphur (6%) in petrolatum for many years; patients have included infants, small children, pregnant and lactating women and persons with neurologic problems. We had never seen an example of systemic toxicity or fatality. . . .!"
12. The use of sulphur in topical preparations is recommended in all of the standard text books of dermatology which I consulted. In particular, the section on topical treatments in "Dermatology" (Braun-Falco, O., et al., p.1156 Springer-Verlag 1991) describes pastes and ointments containing 2, 10 and 20% sulphur, often combined with resorcinol (5%) for several purposes, including use as an antifungal agent.
13. The use of 10% sulphur in either pork fat or cold cream for the treatment of scabies is described by Avila-Romay et al., in a paper entitled "Therapeutic efficacy, secondary effects, and patient acceptability of 10% sulfur in either pork fat or cold cream for the treatment of

scabies," R. *Pediatr Dermatol* 1991; 8:64-6 cited in "Treatment of Skin Disease" (Mark G. Lebwohl, M.D., et al. eds., Mosby 2002).

14. According to the "Textbook of Dermatology" (R.H. Champion et al. eds., p.1461 Blackwell Science 6th ed.), "[s]ulphur has been used for centuries, and sulfur ointment is still employed by some dermatologists. Used excessively, or in high concentration, it may cause irritation, but 10% sulphur in yellow soft paraffin is, in general, safe and effective" for the treatment of scabies. In addition, "topical sulphur-containing preparations have also been shown to be effective in rosacea." *Id.* at 3533.
15. The use of sulphur for the treatment of scabies is described as "safe" and "effective" in "Fitzpatrick's Dermatology in General Medicine" (Irwin M. Freedberg, M.D., et al. eds., p. 2285 McGraw-Hill 6th ed.).
16. The use of sulphur is described in "Dermatopharmacology of Topical Preparations" (Gabard, et al. eds., Springer 2000). In particular, the authors state "[s]ulphur has been used in concentrations of up to 10% in the treatment of acne, rosacea, dandruff and seborrheic conditions. . . ."
17. The possibility of systemic toxicity from the use of topical sulphur is not mentioned in any of the texts that I consulted.
18. I have conducted four data base searches for the association of sulphur with systemic toxicity and found very little of relevance with regard to the systemic toxicity of sulphur. One paper entitled "Toxicity to beef cattle of sulfur in saline well water: a case study" (Beke, G.J. and Hironaka R., *Sci Total Environ* 1991 Jan. 101:281-90) described a disorder in young cows who ingested saline well water with an extremely high sulphur content. The condition resembled bovine polioencephalomalacia and occurred after 2 months of exposure to the well water. It should be noted that the cattle were exposed to the well water over an extended period of time and that the water was ingested by the cattle. Topical application of sulphur containing

products involves neither the ingestion of sulphur nor the extreme exposure discussed in the Beke article.

19. In another paper entitled, "Toxicology of sulfur in ruminants: review" (Kandyliis, K., J Dairy Sci 1984 Oct. 67:2179-87), it was concluded that excessive quantities of dietary sulphur, above 0.3 to 0.4%, as sulfate or elemental sulphur may cause toxic effects and in extreme cases may be fatal when ingested. However, this paper does not teach or suggest that the topical use of sulphur is toxic.
20. A paper entitled "Potentially hazardous sulphur conditions on beef cattle ranches in the United States" (Gould, D.H., et al., J Am Vet Med Assoc 2002 Sept. 221:673-7) analyzed the sulfur content of water and forage samples on various cattle ranches in the United States. The total sulfur intake was estimated for pairs of forage and water samples. Again, this paper taught excessive sulphur intake resulting from the *ingestion* of sulphur by cattle. Topical application of a sulphur compound does not pose the same risks as does ingestion of a sulphur compound.
21. I can state that within my knowledge and experience, topical sulphur containing preparations are used for many different forms of skin complaint and are frequently used in concentrations of up to about 10%. In addition, the use of 3-10% sulphur in topical over the counter drugs has been approved by the Food and Drug Administration and is so listed in the Federal Register (a copy of which is attached hereto as Exhibit A). One of ordinary skill in the art would regard the Federal Register as a reliable and accurate source.
22. Neither I nor to my knowledge my colleagues have encountered systemic toxic side effects

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